REMARKS

1. Introduction

This Amendment is being filed on or before May 4, 2005 in response to the final office mailed on November 4, 2004. Filed simultaneously herewith is a Request for Continued Examination and Petition for a 3-month Extension of Time extending the response date to May 4, 2005, as well as the requisite fees in connection therewith. In light of the foregoing amendment and following remarks, Applicants respectfully request withdrawal of all rejections and a prompt allowance of all pending claims.

The independent claims have been amended to recite mixture, formulations and methods using the same which are derived from tall oil. Support for these amendments may be found in the specification as filed at least at page 6, line 17- page 14, line 17.

2. Relevant Law

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to a skilled artisan to modify the reference or to combine the reference teachings. M.P.E.P. § 2142. Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or references, when combined, must teach or suggest all the claim limitations. *Id.*; and M.P.E.P.§2143.03.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. M.P.E.P. § 2143.01. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. M.P.E.P. §2143.01. Moreover, it is improper to base an obviousness rejection on the argument that the claimed combination is "well within the ordinary skill of the art or within the capabilities of a skilled artisan." *Id.* As recently explained in detail by the Federal Circuit:

> "As noted above, the suggestion to combine requirement is a safeguard against the use of hindsight combinations to negate patentability. While the skill level is a component of the inquiry for a suggestion to combine, a lofty level of skill alone does not suffice to supply a motivation to combine. Otherwise a high level of ordinary skill in an art field would almost always preclude patentable inventions.

> As this court has often noted, invention itself is the process of combining prior art in a nonobvious manner. *See, e.g.*, Richdel, 714 F.2d at 1579; Environmental Designs, 713 F.2d at 698. Therefore, even when the level of skill in the art is high, the Board ***must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination***. *Cf.* Gechter v. Davidson, 116 F.3d 1454, 43 USPQ2d 1030 (Fed. Cir. 1997) (explaining that the Board's opinion must describe the basis for its decision). In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."

In re Rouffet, 149 F.3d 1350, 1359 (Fed. Cir. 1998).

And while it is recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, reliance on knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. *See In re McLaughlin,* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Drawing on hindsight knowledge of the claimed invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction - an illogical and inappropriate process by which to determine patentability. *Sensonics, Inc. v. Aerosonic, Corp.*, 38 USPQ2d 1551 (Fed. Cir. 1996). Thus, where there is no motivation to modify a reference, the rejection has been based on impermissible hindsight and the rejection is improper.

Moreover, "***determination of obviousness can not be based on a combination of components selectively culled from the prior art to fit the parameters of the claimed invention***." *ATD Corp. v. Lydall, Inc.*, 48 USPQ2d 1321 (Fed. Cir. 1998).

3. Rejection of Claims 36-38, 40-46, 48, 50, 52, and 54 Under 35 U.S.C. § 112

Claims 36-38, 40-46, 48, 50, 52, and 54 stand rejected as indefinite for failing to point our and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that "[t]he instant claims are indefinite because they do not end with a period..." Applicants point out that omission of the period was a typographical error which has been corrected by the above amendments. Consequently, Applicants respectfully request withdrawal of this rejection and allowance of these claims.

4. Rejection of Claims 36-55 under 35 U.S.C. § 103

a. The Examiner's Rationale

Claims 36-55 stand rejected as being unpatentable over Sorkin, Jr. ('393), Gamble et al. ('776), Maurel et al. ('924), and Milstein et al. ('230). More specifically, the Examiner states:

> Briefly, compositions comprising phytosterols and policosanols are known in the art (see '393, see the entire article, especially col. 1, lines 5-8; col. 3, lines 11-26; examples 1 and 2; col. 2, lines 27-31 and Table 1; col. 3, Table II). In addition, phytosterols and policosanols are known in the art to be useful as hypocholesterolaemic agents, and thus, a composition comprising both phytosterols and policosanols for use as hypocholesterolaemic agents would have been prima facie obvious to the skilled artisan in the art (see '776, see the entire article, especially Abstract, col. 4, lines 20-28; col. 5, lines 47-56 and col. 9, lines 44-63; '924, see col. 2, lines 33-46 and '230, see col. 1, lines 18-45).
>
> Again, the recitation of the specific wt % of each phytosterol and policosanol in the claimed composition is noted. However, the court has held that merely selecting proportions and ranges is not patentable absent a showing of critically. *In re Russell*, 439 F.2d 1228, 169 USPQ 426 (CCPA 1971). Applicant has not provided any factual evidence of record showing the amounts of each phytosterol and policosanol as recited by the instant claims are critical to the instant invention.

In summary, it is the Examiner's position that policosanols are known in the art, that phytosterols and policosanols are known to have hypocholesterolaemic activity, that all phytosterols and policosanols would be interchangeable, and thus, that the claimed compositions would be obvious to one of ordinary skill in the art.

Applicants respectfully traverse this rejection. The Examiner has failed to establish any of the three criteria which must be met to establish a *prima facie* case of obviousness.

b. The Cited References Fail to Teach or Suggest All of the Limitations of the Rejected Claims

First, the prior art references relied upon by the Examiner do not, in combination, teach or suggest all of the limitations of the rejected claims. As amended, each of the currently pending claims recite a mixture, formulation or method using such mixture or formulation which is derived from tall oils. None of the references cited by the Examiner teach mixtures, formulations or methods utilizing such mixture or formulation derived from *tall oil*. To the extent the Examiner relies on the ordinary skill in the art to modify such references, such reliance is improper and is discussed in more detail below.

Moreover, the Examiner relies on *In re Russell* for the proposition that recitation of specific wt% of each phytosterol and policosanol is insufficient to confer patentability in the absence of a showing of criticality. As an initial point, applicants respectfully point out that *In re Russell* actually holds the converse, that when applicant has shown unexpected results, a prima facie case of obviousness is overcome. That is, in *Russell*, the patent office had shown that a prior art reference disclosed all of the ingredients of the claimed composition and essentially all of the claimed proportions of the composition. Thus, the patent office had presented a strong prima facie case of obviousness which the applicants were able to overcome by a showing of surprising results. The *Russell* holding **did not** say that when the prior art only discloses the components but not the proportions that a showing of surprising results is required. In contrast, the prior art relied upon by the Examiner in this application do not disclose the proportions recited in the claims. Significantly, in light of the amendments to the claims, the prior art cited by the Examiner do not even disclose the components.

Finally, the Examiner has completely failed to address limitations present in the dependent claims, including for example, dosage amounts and total approximate weight percentages of the primary aliphatic higher alcohols. The Examiner has shown no prior art reference whatsoever disclosing such limitations nor has the Examiner provided any principle known to one of ordinary skill in the art which would suggest modification of the cited references to achieve such limitations.

c. There is No Suggestion In the Prior Art to Combine or Modify the Cited References.

Second, the Examiner has failed to point out those sections of the prior art references relied upon which suggest the combination and/or modification of the cited references. Rather, the Examiner appears to rely solely, and improperly, upon an assertion that the claimed invention would have been well within the ordinary skill of the art at the time the claimed invention was made. M.P.E.P. § 2143.01 (stating that claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish prima facie obviousness).

In fact, applicants respectfully point out that the art clearly shows that policosanols from different natural sources are not readily interchangeable, nor do they exhibit the same therapeutic effects. In fact the art shows that policosanols from different origins exhibit different therapeutic effects, including specifically different hipocholesterolemic effects. For example, U.S. Patent No. 6,465,526 discloses bee wax and sugar cane policosanols, which were tested in several pharmacological applications. In one such test, the hypocholesterolaemic activity of these policosanols was investigated. Example 11 of the '526 patent discusses these tests, as follows:

> EXAMPLE 11
>
> Is done a comparative study between the properties of the natural mixtures of higher primary aliphatic alcohols obtained from bee wax (M.H.A.A.B.W.), object of the present invention, and that of the higher primary aliphatic alcohols obtained from sugar cane wax (EPC 0 488 928) (named M.H.A.A.S.C.W. since this moment). This study permit the possibility of establishing that both mixtures not only differs in the number of alcohols and in the relative composition of the alcohols present in both of them, but also, in its pharmacological profile, in different experimental models traditionally used in the pharmacological screening, are also different. For that reason are developed the experiments that are described as follows:
> a) anti-inflamatory effect: In order to corroborate the anti-inflamatory effect of both mixtures, the models of pleuresy by carragenine and granule by cotton were used, doses of 100 and 200 mg/kg, respectively, were used.
> b) antiulcer effect: In order to corroborate the antiulcer effect of both mixtures it was used the experimental methodology previously described

in Example 8 of the present invention, using doses of 25 mg/kg of corporal weight for both mixtures.
c) hipolipidemic effect: Male New Zealand rabbits were used and divided in the following groups a) controls, b) M.H.A.A.B.W. (5 mg/kg) and c) M.H.A.A.S.C.W. (5 mg/kg) administered orally during 1 month. Each 15 days blood samples were taken in order to determine the lipidic parameters (total cholesterol, triglycerides, HDL-C, LDL-C and VLDL-C).
d) antiischemic effect: For the analysis of both mixtures over the cerebral ischemia it was used the model in which cerebral ischemia is provoked in Mongolian gerbils by carotide ligature. Female Mongolian gerbils, of 60 to 80 g of weight, were used that were adapted to laboratory conditions for free access to food and water. Both mixtures were administered by i.p. route using for this purposes a suspension in a 2% Tween 20/water vehicle. The animals were distributed in the following experimental groups: 1) control (vehicle 2% Tween 20/water), 2) M.H.A.A.B.W. (200 mg/kg) and 3) M.H.A.A.S.C.W. (200 mg/kg).

The ligature of the left common carotide was done anaesthetizing the animals with an ether atmosphere. The animals were observed for 24 h, registering the appearance of clinical symptoms of cerebral damage, such as circling, rolling and convulsions, as well as the number of deaths produced during the experiment.
e) antiplatelet aggregation effect: In order to corroborate the effect of both mixtures on the platelet aggregation in rats, induced by ADP or collagen, a number of male Sprague Dawley rats, weighing 250-350 g, were used. Each one of the mixtures was administered orally as a suspension in an acacia gum/water vehicle (1 mL/100 g body weight) for 4 weeks using gastric gavage. The animals were randomly distributed in 3 experimental groupsa) control (only received vehicle), b) M.H.A.A.B.W. (25 mg/kg) and c) M.H.A.A.S.C.W. (25 mg/kg).
For the development of the platelet aggregation assay, the rats were anaesthetized in ether atmosphere. After the abdomen is open, blood was extracted (5 mL) from cava vein and mixed with 3.8% sodium citrate (1 volume of sodium citrate for 9 volumes of blood). The platelet rich plasma (PRP) was obtained by blood centifugation and the platelet poor plasma (PPP) was obtained by centrifugation of PRP aliquots at 330 g for 15 min. Platelet aggregation was induced by ADP or collagen and was registered in a Payton aggregometer.
f) antithrombotic effect: For the study of the antithrombotic effect the venous thrombosis model was used. The following treatments were administered for these purposes: 1) control, 2, 3, 4) M.H.A.A.B.W. (25, 50 and 100 mg/kg), respectively and 5, 6, 7) M.H.A.A.S.C.W. 25, 50 and 100 mg/kg) respectively.

Rats were anaesthetized with sodium phentobarbital (40 mg/kg) by i.p. route. Later on, were injected with hipotonic saline solution (0.22% NaCl)

(1 mL/100 g body weight) by the femoral vein. A minute later, the abdomen was opened and the cava vein was exposed, isolated and ligatured passing a thread through the vein. The abdomen was closed, provisionally, for 10 min, later on, it was reopened and the cava vein was ligatured again, 2 cm below the first ligature. Immediately, it was removed and longitudinally opened, the thrombo was removed and was set in a humid oven at room temperature, being weighed 1 hour later.
The results obtained after the development of all these pharmacological assays are summarized in Table 17.

TABLE 17

Comparative effect between the natural mixture of alcohols obtained from bee wax and those obtained from sugar cane wax

Assay	M.H.A.A.S.C.W.	M.H.A.A.B.W.
Anti-inflamatory	+	-
hipolipidemic effect	-	+++
antiischemic	+	+++
antiulcer	+++	+
antiplatetlet aggregation	-	+
antithrombotic	-	+

with activity:
(+) discrete
(++) moderated
(+++) higher
(-) without any activity

As can be observed, from these results, the pharmacological properties of both natural mixtures of higher primary aliphatic alcohols are differents, only in the antiulcer effect both mixtures exhibit activity, but, as can be shown in the Table, the effect of the mixture of alcohols obtained from bee wax (M.H.A.A.B.W.) is much more effective than that obtained from sugar cane wax (M.H.A.A.S.C.W.).

'526 patent, col. 12, line 29 – col. 14, line 5.

The art further shows that policosanols from specific, natural origins have different therapeutic, including hypocholesterolaemic, activity than synthetic higher alcohols, such as pure hexacosanol and pure octacosanol. Specifically, U.S. Patent No. 5,663,156 discloses that pure hexacosanol and pure octacosanol have no statistically significant cholesterol-lowering effect, as follows:

EXAMPLE 11

Male New Zealand rabbits were distributed randomly in 4 groups: a control group (only receiving vehicle by gastric gavage) and 3 groups treated M.H.P.A.A., octacosanol and hexacosanol, respectively at 5 mg/kg. Serum lipid profile was determined at baseline and 30 days before

treatment. M.H.P.A.A. decreased significantly total cholesterol and LDL-C. Moreover, levels of cholesterol, LDL-C and triglycerides of M.H.P.A.A.-treated rabbits were significantly lower than those of the controls. Nevertheless, the changes on serum lipid profile occurred in groups treated with octacosanol or hexacosanol did not achieve statistical significance as is shown in Table 13.

TABLE 13

Effects of M.H.P.A.A., octaconsanol and hexacosanol on serum lipid profile (mmol/L) of New Zealand normocholesterolemic rabbits (mean values)

Group	Dose (mg/kg)	Baseline	After treatment
Total cholesterol			
Controls	0	2.5	2.3
M.H.P.A.A.	5	2.8	1.6 *+
Octacosanol	5	2.7	2.2
Hexacosanol	5	2.6	2.4
LDL-C			
Control	0	1.5	1.2
M.H.P.A.A.	5	1.3	0.6 *+
Octacosanol	5	1.4	0.9
Hexacosanol	5	1.5	1.0
Triglycerides			
Control	0	0.80	0.82
M.H.P.A.A.	5	0.78	0.55 *
Octacosanol	5	0.77	0.70
Hexacosanol	5	0.80	0.78

* $p < 0.05$ comparison with controls (Mann Whitney U test)

+ $p < 0.05$ comparison with baseline (Wilcoxon)

'156 patent, col. 12, line 49 – col. 13, line 22.

Thus, the art clearly demonstrates that the policosanol composition profile and source are critical in determining hypocholesterolaemic activity. Thus, it would not have been obvious to one of ordinary skill in the art to use policosanols and phytosterols and mixtures thereof derived from tall oil to achieve hipocholesterolemic benefits.

d. There is No Reasonable Expectation of Success in Modifying the Cited References.

In view of the discussion in the previous section, it is clear that there would be no reasonable expectation of success in achieving hipocholesterolemic activity with policosoanl and phytosterol mixtures wherein such mixtures are derived from tall oil. At best, the fact that certain naturally occurring policosanols show a hipocholesterolemic effect would only suggest trying or testing any or all such naturally occurring compounds. That is, at best, the prior art suggests that it is "obvious to try" such combinations/modifications. Only where the prior art contains a clear suggestion to combine or modify references can such an "obvious to try" suggestion result in a prima facie case of obviousness. That is not the case here. In the present application, the prior art suggest at most, without any other suggestion or motivation, that it may be "obvious to try" policosanols from tall oil. It is well established that such a motivation is improper and cannot form the basis for a prima facie case of obviousness.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: May 4, 2005

Respectfully submitted,

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